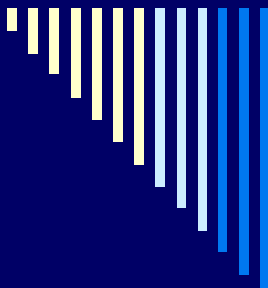



BMT Tandem Meeting Regulatory Issues Session

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Guidance for Industry

Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies

January 17, 2007

72 FR 1999



Draft Guidance

- For comment purposes only
 - Comment period ends April 17, 2007
 - Does not establish legally enforceable responsibilities
 - Represents FDA's current thinking
 - Recommendations, unless specific regulatory or statutory requirements cited
 - Can use an alternative approach
-



Purpose

- Recommends ways for cord bank to apply for licensure for specified indications
 - Explains applicable regulations in Title 21 of the Code of Federal Regulations
 - Provides other information about the manufacture of HPC-C and how to comply with the applicable regulatory requirements
-



Scope

- Covers cord blood products that are:
 - Minimally manipulated; and
 - Intended for hematopoietic reconstitution in patients with hematological malignancies; and
 - Intended to be used in recipients unrelated to the donor
 - Does not cover:
 - PBSC
 - Other cord blood products (e.g. more than minimally manipulated, and/or for other indications)
 - Cord blood for autologous/family-related use (though encourage following these recommendations)
-



Why is the indication limited?

- Cord blood regulated as HCT/P
 - Homologous use broadly defined – hematopoietic reconstitution
 - Preponderance of data submitted to docket describing cord blood transplant outcomes in patients with hematologic malignancies (approximately 65-70%)
 - Numerous other indications – much less data (all genetic disease 25%, SAA/FA 5%)
-



Use of this Guidance

- Demonstrate that you have followed recommendations
 - You may modify any procedure in guidance
 - Present evidence demonstrating that modification will provide assurances of safety, purity, potency, and effectiveness
 - License would apply to HPC-C manufactured after approval, and to HPC-C previously manufactured in accordance with the information provided in the license where documentation provided to demonstrate comparability
 - You may submit BLA containing your own data from clinical studies
-



Background

- History of promulgation of HCT/P regulations
 - Summary of 1998 FR notice: Request for Proposed Standards
 - Summary of 2003 BRMAC cord blood meeting
 - Determination that data submitted to docket and published literature permit development of BLA recommendations
-



Applicable Regulatory Requirements

- Prelicense inspection
 - 21 CFR Parts 210 and 211 (CGMP), 600 (Biological Products: General), 610 (Biological Products Standards), 201 and 610 Subpart G (labeling), 202 (advertising)
 - 21 CFR 1271 HCT/P regulations
 - More specific regs supercede more general
 - Compliance with CGMP would result in compliance with applicable CGTP requirements, with some exceptions
 - Use Section VII of Guidance as a reference
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License Application Procedure

- Form FDA 356h – Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use
 - Where to submit – Document Control Center (address provided)
 - What information to include
 - What action FDA will take
-



Information to include

- Index
 - Representative draft labeling
 - Summary of information submitted
 - CMC – 21 CFR 314.50(d); § 601.2
 - Full description of manufacturing process and SOPs for critical procedures, assays
 - Summary validation data
 - Establishment description – § 600.10
 - Other attachments, including citation to data in docket
-



What action will FDA take?

- Review application
 - Schedule prelicense inspection as soon as possible after receiving complete application
 - If application not complete, identify/advise you of additional information that you will need to submit
-



Chemistry, Manufacturing and Controls (CMC) Section

- HPC-C Description and Characterization
 - Manufacturers
 - Methods of Manufacturing
 - Container Closure System
 - Environmental Assessment
 - Methods Validation/Verification
 - Labeling
-



Required and recommended test results

- Safety: ID testing, Sterility testing, Hb
- Purity and potency (pre-cryopreservation)
 - $\text{TNC} \geq 5.0 \times 10^8/\text{HPC-C}$
 - Based on 20 kg recipient dose of $\geq 2.5 \times 10^7/\text{kg}$ and 70% post-thaw recovery = $1.7 \times 10^7/\text{kg}$
 - Viable nucleated cells $\geq 85\%$
 - Viable CD34+ cells $\geq 1.25 \times 10^6/\text{HPC-C}$
 - Based on CD34+ cells $\geq 0.25\%$ prior to freezing
- Identity: HLA typing, confirmatory typing using attached segment, ABO/Rh



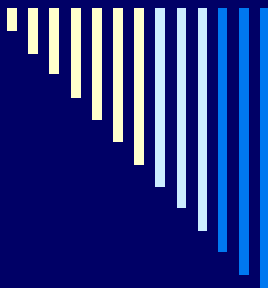
Manufacturer information

- Identification
 - Includes FDA registration number, contract manufacturers (collection sites, labs performing RCDAD and product sterility testing)
 - Floor diagrams
 - Not necessary for collection sites
 - Contamination precautions
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Methods of manufacturing

- SOPs to submit
 - Collection, processing, selection, shipping and handling (including thawing and preparation for administration, salvage)
 - Validation data summary
 - Recommend data from 3 consecutive, separate HPC-Cs
-



HPC-C manufactured using different procedures

- Separate validation summary including data demonstrating:
 - Comparability between the previously manufactured HPC-C and those manufactured currently
 - Product characteristics
 - Clinical outcome data
 - References on comparability in Guidance
 - Evidence that methods, facilities, and controls used for manufacture conform to CGMP and other applicable regulatory requirements
-



Other CMC information

- Description of container closure system
 - Can reference NDA, 510(k), or MF
 - Provide evidence of container and closure integrity for duration of proposed storage period
 - Environmental assessment – 21 CFR Part 25
 - May submit request for categorical exclusion
 - Methods validation/verification
 - Infectious disease tests – licensed/approved/cleared
 - Other tests – sterility, TNC, HLA, ABO/Rh, other
 - Labeling – see guidance Section VII.B.2
-



Establishment Description

- General Information
 - Floor diagram
 - Description of processing areas
 - Activities in adjacent areas
 - Product, personnel, equipment and waste flows
 - Specific Systems
 - Water, HVAC, facility controls, computer systems
 - Contamination/Cross-Contamination Issues
 - Equipment cleaning, air handling, decontamination
-



Guidance on Applicable Regulations

- Describes applicable provisions in the HCT/P regulations, CGMPs, biologics regulations in 21 CFR Parts 600 - 680
 - Formatted to follow CGMP subparts
 - Establishment Registration and Listing
 - Current Good Manufacturing Practice (CGMP) and Current Good Tissue Practice (CGTP)
 - Label and Labeling content
 - Holding and Distribution
 - Laboratory Controls
 - Records and Reports
 - Failure investigations, tracking, complaints, returned and salvaged HPC-C
-



Postmarketing Activities

- Clinical Outcome Data Collection
 - Recommend analysis of clinical data from transplant centers as quality indicator
 - Should evaluate data to determine whether AEs or other unexpected outcomes may be due to manufacturing problems
 - Changes to be Reported (21 CFR 601.12)
 - Adverse Experience Reporting (21 CFR 600.80)
 - Biologic Product Deviation Reporting (21 CFR 600.14(d))
-



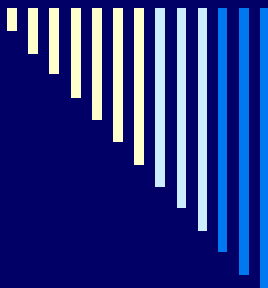
Next steps

- Review and address comments
 - ? Public meeting
 - Finalize Guidance
 - Intend to include date for implementation of IND/BLA requirement (ending period of IND enforcement discretion)
 - License applications accepted at any time
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Device Final Rule and Special Control Guidance

- Rule classifies cord blood processing system and container into class II (special controls) - published 1/31/07
 - Guidance for Industry: Class II Special Controls Guidance Document - Cord Blood Processing Systems and Storage Containers
 - Describes means by which the cord blood processing system and container may comply with the requirement of special controls for class II devices
 - Immediately in effect but subject to comment in accordance with the agency's good guidance practices
-



Guidance: HCT/Ps Tested Using Pooled Specimens or Diagnostic Tests

- Published 1/23/07; for immediate implementation
 - Comments to the docket accepted
 - For HCT/Ps recovered after 5/25/06 to 30 days after publication
 - Addresses:
 - Distributed HCT/Ps and those in inventory
 - Need for HCT/P deviation reports if distributed
 - Retesting/labeling for future distribution of HCT/Ps in inventory
-



Testing Guidance – cont.

- FDA is exercising enforcement discretion to allow distribution of these HCT/P
- Limited to the two testing deficiencies
- Pertains to recently regulated living donor HCT/P (hematopoietic stem/progenitor cells and reproductive cells and tissues)
- For distributed HCT/Ps, deviation reports only required for hematopoietic stem cells from first or second degree blood relatives
 - One report for all affected HCT/Ps



Testing Guidance: HCT/P Retesting Before Distribution

- Recommend using original donor sample
 - Tested in accordance with the manufacturer's instructions and found negative/nonreactive
 - New specimen OK
- If retesting not feasible
 - Documentation recommended in files
 - Physician notification
 - Labeled "WARNING: Advise patient of communicable disease risks"



Testing Guidance: Retesting Donors

- If you cannot retest the donor, you can distribute these in-inventory HCT/P:
 - Hematopoietic stem/progenitor cells (other than autologous)
 - Cryopreserved embryos formed using 3rd party gametes
- If you cannot retest the donor, you cannot distribute cryopreserved semen or oocytes from anonymous or directed donors